Memo: Pharmacology/Toxicology Review

Pharmacology/Toxicology NDA 21-213
Mevacor Daily 20 mg/(OTC lovastatin)/Merck

Introduction: Merck is proposing to market Mevacor (lovastatin) 20 mg/day in an OTC setting as an adjunct to diet and exercise in individuals with LDL 130-170 mg/dl and multiple risk factors for heart disease. Mevacor OTC is proposed for men ≥45 years and post-menopausal women ≥55 years. Mevacor was the first approved HMG-CoA reductase inhibitor (statin) and has been marketed as a prescription-only drug since 1987 to lower cholesterol. The weight of evidence from two decades of animal reproductive/developmental toxicity studies demonstrates that Mevacor has the potential to induce skeletal malformations and developmental delays in the fetus/neonate irrespective of the presence of maternal toxicity. This differs from Merck's current interpretation of the nonclinical developmental studies and served as a basis for their request for a change in pregnancy category designation in the Mevacor label.

HMG-CoA reductase is the rate limiting enzyme in de novo cholesterol biosynthesis which converts hydroxymethylglutaryl-CoA to mevalonic acid. Lovastatin is a lactone pro-drug that is converted to the active open acid form by plasma and tissue esterases. Merck proposes that fetal skeletal malformations observed in rats given high doses of Mevacor (≥400 mg/kg/day) are secondary to maternal toxicity produced early during gestation and that this toxicity is pharmacologically based. Therefore studies with co-administered mevalonate; the metabolic product of HMG-CoA reductase were performed to eliminate the maternal toxicity and hence prevent the fetal skeletal malformations observed with Mevacor. Additional studies using subcutaneous instead of oral administration of Mevacor prevented the maternal toxicity (forestomach acanthosis, hyperkeratosis) and the skeletal anomalies according to the sponsor. Merck proposes that any developmental delays observed in post-natal rats was spurious and occurred at significant multiples of clinical exposures and therefore are not a clinical concern. However this conclusion is based on a limited post-natal neurodevelopmental assessment following direct dosing of neonatal rats which inadequately addressed the original concern for post-natal neurodevelopmental abnormalities because of the limited scope of the study design.

The original nonclinical safety assessment of lovastatin included developmental toxicity studies (fertility, embryo-fetal, and pre- and postnatal development) in rat and rabbit with lovastatin and its active metabolite (open acid form). Additional developmental studies were performed following market approval in 1987 through 1999. In 1999 Merck submitted NDA 21-213 for a 10 mg nonprescription form of lovastatin for the treatment of elevated cholesterol for primary prevention of coronary heart disease. Prescription Mevacor is labeled as Pregnancy Category X as are all of the statins based on the findings in animals and the established inhibitory effects on cholesterol synthesis by members of this drug class. The Pregnancy Category X designation is equivalent to a contraindication for use of a product during pregnancy based on studies in animals or experience in humans demonstrating adverse fetal effects whereby the fetal risk

outweighs the benefit of drug exposure to the mother. The battery of reproductive toxicity studies conducted for lovastatin using standard study designs inadequately assess potential drug effects on neuronal developmental processes that occur in the post-natal rat (e.g. myelination) and during the second and third trimester in humans. This contention was supported by the CDER PTCC Reprotoxicity Committee and members of the Pharmacology/ Toxicology Senior Leadership Team. Both groups recommended additional postnatal neurodevelopmental studies to address this data gap based on findings in the prior developmental studies and the potential clinical concern.

A neurodevelopmental toxicity study using direct dosing of neonatal rats was recommended to include evaluations of exposure, establishment of a NOEL (no observed effect level), and detailed brain histology and behavioral/developmental/functional assessments. Merck submitted a dose range finding study and definitive study protocols on 5/22/01. The Division and the CDER PTCC Reprotoxicity Committee provided detailed feedback on the protocol design in advice letters of 7/01, 5/02, 11/02 and 10/03. The final study reports were submitted for review 4/04.

Nonclinical Safety Issue Relevant to Clinical Use: Clinical data obtained during pregnancy is very limited, but does exist. The numbers of cases are too few to demonstrate any correlation; however the pregnancy outcomes do not allay concern. An April 8, 2004 letter to NEJM examining adverse event reports (AEs) in the FDA AERS database from 1987-2001 finds 5 cases associated with CNS and limb deficiency anomalies from 52 cases of lovastatin exposure during pregnancy. These abnormalities are exceedingly rare in the general population. In 2/5 of these cases pregnant women were exposed to doses at or below the proposed OTC dose of 20 mg/day.

The Office of Drug Safety (ODS) was consulted to update the pregnancy outcome data from the FDA AERS database of *in utero* exposure to statins; 25/195 cases were reported for lovastatin. These 25 cases involved 9 elective terminations, 4 spontaneous terminations, 1 unknown outcome and 11 live births. Among the live births 6 cases had normal outcomes, 4 had birth defects and 1 had other complications as outlined in the following table. Data were available on one of the elective terminations.

Live Births with Defects	Findings	Lovastatin Dose	Prenatal Exposure
Case 1	Malformations: musculoskeletal-upper extremity, dentofacial & breast, dysmorphic features-ptosis, torticollis, hemangioma, joint disorder	unknown	~2 weeks
Case 2	Left hand tag, non-functional thumb, holoprosencephaly, hydrocephalus	40 mg	~6 weeks
Case 3	Aortic hypoplasia, atrial & ventricular septal defect, 2^0 cerebral dysfunction, mortality day 2	40 mg	~5 weeks
Case 4	Right auditory canal absent [concomittent meds: ethinyl estradiol/ethynodial diacetate,	unknown	~8 weeks

	pseudoephedrine, acetaminophen]		
Case 5	5 year old: attention deficit disorder, seizures, ataxia, abnormal fine motor movement	unknown	~ 8 weeks
Data on elective terminations			
Case 1	Spina bifida, hydrocephalus	20 mg	3 -18 weeks

The most common birth defects in the US are cardiac and circulatory at 260.4/100,000 live births followed by musculoskeletal and connective tissue defects at 239.4/100,000 live births (~0.2%) according to the National Vital Statistics System [http://www.cdc.gov/nchs/data/nvsr/nvsr49/nvsr49_01.pdf]. The number of reported exposures is small and the true rate of occurrence for the reported defects is unknown because these reported cases were spontaneous reports to the AERS database. A causal association between *in utero* statin exposure and identified birth defects cannot be made based on the current information. ODS suggests that latent effects such as birth defects are best captured through a registry system which is not available for statins.

Nonclinical studies: Animal reproductive toxicity studies are designed to address the potential for adverse developmental (*in utero*) risk. Standard reproductive study designs focus on *in utero* exposure before/during conception (Segment I), organogenesis (Segment II) and through lactation (Segment III). These studies are designed to assess acute toxic effects with some sensitivity. However they are not designed to evaluate subtle or long-term effects.

Skeletal/Developmental Abnormalities: Merck contends that reproductive studies performed 1980-1999 revealed skeletal anomalies in rats at maternally toxic doses (≥400 mg/kg/day). The observed fetal skeletal abnormalities are likely attributable to fetal nutritional deficits due to reductions in maternal food intake and body weight, secondary to acute maternal forestomach edema/inflammation leading to acanthosis/hyperkeratosis with repeated oral dosing. The forestomach is an organ specific to the rat and therefore this toxicity is not relevant to humans. Although the cellular mechanism is unknown, Merck suggests that marked up-regulation of the forestomach HMG-CoA reductase in the modified squamous epithelium is possible. This has been demonstrated in rodent hepatocytes following lovastatin treatment (PNAS 85:5264-5268, 1988; Fd Chem Toxic 29(9):621-628, 1991). Merck contends that the HMG CoA reductase up-regulation resulting in forestomach histopathology in the rat is reversible with mevalonate co-administration, substantiating the pharmacologic basis of the lovastatin induced effect on the rodent forestomach. However, maternal mortality during gestation is observed with co-administration of mevalonate. It appears that the mortality is a result of esophageal erosion/perforation which is usually indicative of a gavage error; however, it is only the mevalonate treated dose groups that have this finding which is reproduced in two separate studies. There are fetal skeletal findings in the mevalonic acid co-administered groups consistent with the other reprotoxicity studies with lovastatin alone. Merck's basis for establishing that fetal skeletal anomalies are the result of maternal toxicity follows: 1) Elimination of maternal toxicity by alternate dosing regimens (e.g. SC to avoid forestomach toxicity seen with oral administration) eliminates all fetal skeletal abnormalities despite maintaining comparable or greater maternal and fetal drug exposure levels; 2) The dose response for fetal skeletal abnormalities is identical to that for

incidence and severity of maternal toxicity. This is consistent with a literature report that dietary nutrient deficiencies in rats can produce vertebral, rib and sternebral malformations; 3) Maternal, embryonic, and fetal exposures to lovastatin during the critical period for osteogenesis (GD 15) do not correlate with the presence of skeletal abnormalities; 4) Suppression of fetal mevalonate concentration does not correlate with the presence of skeletal abnormalities.

Based on the animal data reviewed over the past 20 years (1980-1999) fetal toxicity including mortality, body weight decrements, skeletal malformation and behavioral/learning delays in the absence of maternal toxicity was observed at drug exposures comparable to the low therapeutic dose range (10-20 mg/day). The Division's interpretation of the reproductive toxicity findings with Mevacor differ from Merck.

Selected Lovastatin Reprotoxicity Studies	**Route**	**Doses (m/k/d)**	**Maternal NOAEL (m/k/d)**	**Exposure Multiple***	Rat Fetal/Neonate Findings+				
					Death	**Skeletal Malformations**	**Develop-mental Delays**	**Decrease Weight**	**External/ Visceral Malformations**
Segment I (Dosing 15 Days prior to mating through Gestation Day 20)									
1.	Oral	8,80,800	80 8	60X 6X	√	√	√	√	√
2.	Oral	2,20,200	20 2	15X 2X	√			√	
3.	Oral	15,240	15	5X	√			√	√
Segment II (Dosing Gestation Day 6-20)									
4.	Oral	8,80,800	80	60X		√			
5.	SC Oral	12.5,25 400	≤25	<1X	√	√ @12.5 incomplete ossification	√	√	
6.	Oral	100,200, 400,800	100	75X		√		√	
7.	Oral	100,200, 400,800	100	75X		incomplete ossification		√	
Segment III (Dosing Gestation Day 15-Lactation Day 21)									
8.	Oral	2,20,200	20	15X	√		√		

* OTC therapeutic dose=20 mg/day=$AUC_{0\text{-}24h}$=30±15 ng h/ml ; + No maternal toxicity defined as >10% decrease in body weight gain or forestomach toxicity

At ≤5 X therapeutic exposure following a 20 mg/day lovastatin dose, fetal mortality, and decreased body weight is observed. At therapeutic exposures ≥6X following a 20 mg/day dose neonatal developmental delays are observed in free-fall righting reflex, negative geotaxis, auditory startle response, swimming, and reduced latency in the open field test, and incomplete skeletal ossification is seen. At higher exposures of >25X therapeutic exposure, skeletal malformations are observed consisting of increased supernumerary ribs, incomplete bone ossification, and wavy ribs. Animal studies have indicated that Mevacor (lactone) crosses the placenta and is secreted in milk compared to plasma (1:1.5). The cholesterol source in rat embryos is obtained from the yolk sac or placenta (maternal source); de novo synthesis contributes a minor portion of fetal cholesterol. Since lovastatin and other hydrophobic HMG CoA reductase inhibitors can enter fetal circulation there is still a clinical concern for fetal findings following exposure

during organogenesis. A rat maternal NOAEL=80 mg/kg/day (AUC=1900 ng h/ml on GD 20) is suggested based on the data presented. Fetal/F1 pup mortality, decreased weight gain, skeletal findings (wavy ribs) and incomplete ossification are observed reproducibly in prior reprotoxicity studies in litters exposed to 2-80 mg/kg/day, but are unexplained. Developmental/behavioral effects showed a similar pattern. This would suggest a rat developmental NOAEL<2 mg/kg/day (less than clinical exposure at 20 mg/day based on body surface area).

The majority of studies were performed in rat however similar effects were seen in a limited number of studies in rabbits and mice. Rabbits show a developmental NOAEL at ≤ 5 mg/kg/day (or 60 mg/m^2 providing a 5X safety margin to the therapeutic dose of 20 mg/day=12 mg/m^2). In rabbit visceral abnormalities are seen at 15 mg/kg/day (15X exposure following a 20 mg/day clinical dose) with higher doses of 25 mg/kg/day being lethal in dams. Rat maternal drug transfer is 20-40% whereas in rabbit it is only 2%. Similarly, in an oral mouse Segment II study testing 8, 80, 800 mg/kg/day, maternal toxicity is not evident but skeletal malformations are increased at 80 and 800 mg/kg/day by 6/24, 8/24 litters respectively versus 4/24 control litters. Visceral variations in 3/24 litters given 800 mg/kg/day versus 1/24 control litters were observed. A mouse developmental NOAEL= 8 mg/kg/day (or 24 mg/m^2 providing a 2X safety margin to the therapeutic dose of 20 mg/day=12 mg/m^2) was established.

Studies of lovastatin co-administered with either mevalonic acid or cholesterol appeared to attenuate the more severe fetal malformations, however some fetal skeletal toxicity is observed (wavy ribs, incomplete ossification etc.) despite the addition of mevalonate. This supports the original conclusion that the fetal findings result from disruption of cholesterol biosynthesis as an extension of the pharmacologic activity of lovastatin. Merck concludes that fetotoxic effects at maternally toxic doses of lovastatin are not a function of reduced cholesterol biosynthesis (decreased fetal plasma mevalonate). Rather they conclude that fetotoxicity at maternally toxic doses of Mevacor is a function of reduced cholesterol biosynthesis in the forestomach. HMG-CoA reductase required for mevalonate synthesis is tissue bound (endoplasmic reticulum). Hence, tissue levels of mevalonate could be different than plasma levels, as suggested by Merck's attribution of reduced rat forestomach mevalonate as causative of maternal toxicity during developmental studies.

Lovastatin	Plasma Mevalonate Levels (ng/ml)	
Dose/Route (mg/kg/day)	Maternal	Fetal
Oral 80	10	29
Oral 400	11	45
SC 12.5	8	36
SC 25	11	39

Differences in the timing of developmental processes across species are not generally addressed in interpretation of standard reproductive toxicology studies. This becomes important in particular developmental events. For example, myelination occurs in the rat during postnatal weeks 2-4. The standard reprotoxicity test battery does not extensively evaluate postnatal developmental processes, particularly neurological maturation to any

significant effect. The majority of myelination occurs in humans during the second and third trimester. This implies that the nonclinical animal studies with standard designs did not evaluate this process at all. Furthermore, limited first trimester clinical exposure would also not be relevant to address this potential risk. Therefore, a limited postnatal neurodevelopmental assessment following direct dosing in neonatal rats was recommended. The results of this study suggested a NOAEL of 5 mg/kg/day (20X clinical exposure following a 20 mg/day dose based on AUC) based on a delay in learning/short-term memory assessment (passive avoidance test) at 10 mg/kg/day. The neurological evaluation was minimal and standard general toxicology endpoints were not assessed in the neonatal rat following direct dosing. The study represents the only "new" data provided by Merck which still does not significantly address the concern originally identified. Merck included a passive avoidance test as the sole measure of cognitive function in the direct dosed neonatal rat study. The Agency suggested on several occasions that a more sensitive test of learning and memory in which a learning acquisition curve can be demonstrated (e.g. complex water maze) was preferred. The neonatal rat study was designed to evaluate acute toxic effects on neurologic development, but does not assess delayed effects of a developmental insult because in a neonate, organ structure is already complete. In order to assess this, dosing would have to encompass a longer period of exposure (e.g. *in utero* through weaning).

Conclusion: Extensive reproductive toxicology studies with lovastatin performed from 1980-1999 using standard study designs demonstrate consistent findings of fetal mortality, body weight decrements, skeletal malformations, and behavioral/learning delays in the absence of maternal toxicity. Merck suggests that the skeletal malformations are a function of maternal forestomach toxicity. Based on the well established effect of statins on cholesterol synthesis, behavioral/learning delays in prior developmental studies and the knowledge that major neurodevelopment occurs postnatal in the rat, additional neurodevelopmental assessments of lovastatin were recommended. A limited neurodevelopmental assessment following direct dosing of neonatal rats was performed which suggests a no observed adverse effect level (NOAEL) of 5 mg/kg/day (exposure 20X a clinical dose of 20 mg/day based on AUC). This is based on a delay in a learning/short-term memory assessment (passive avoidance test) at 10 mg/kg/day. This neonatal rat study was designed to evaluate an acute developmental insult and is limited in the scope of its evaluation to address the developmental concerns outlined. This neonatal rat study was the only new information submitted in support of the proposed change in pregnancy category and to address the potential fetal/neonatal clinical concerns. Previous developmental studies have shown neonatal developmental delays in reflexes; free-fall righting, negative geotaxis, auditory startle in addition to delays in swimming and reduced latency in the open field test at exposures at approximately $\geq$ 6X clinical exposure following a 20 mg/day Mevacor dose. At higher exposures (>25X) skeletal malformations occur. Generally fetal mortality and decreased body weight are observed at the proposed clinical exposure ($\leq$5X clinical exposure following 20 mg/day Mevacor). However some of these developmental studies have shown these effects at exposures less than clinical exposure following a 20 mg/day Mevacor dose. Therefore risk to the fetus can not be excluded following clinical exposure and Mevacor should remain contraindicated during pregnancy.

Abbreviations: NOAEL-no observed adverse effect level, GD-gestation day, AUC-area under the curve, NOEL-no observed effect level, CHD-coronary heart disease, NEJM-New England Journal of Medicine, SC-subcutaneous, OTC-over the counter.